Calcium Channel Blockade to Prevent Stroke in Hypertension

A Meta-Analysis of 13 Studies With 103,793 Subjects

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Background: The possibility that specific antihypertensive treatments may prevent the occurrence of stroke more effectively than other treatments remains unproved. We undertook a meta-analysis to assess whether calcium channel blockers (CCBs) are associated with a lesser risk of stroke as compared with other antihypertensive drugs.

Methods: Through Medline we identified 13 major studies conducted in hypertensive subjects for a total of 103,793 subjects. Overall, there were 4040 incident cases of stroke, 1789 among 43,053 subjects randomized to CCBs and 2251 among 60,740 subjects randomized to different antihypertensive drugs.

Results: Considering all 13 trials, a pooled reduction in the risk of stroke was observed among subjects allocated to CCBs (odds ratio 0.90, 95% confidence interval [95% CI] 0.84–0.96; $P = .002$). The risk of stroke was significantly lower among subjects allocated to dihydropyridine CCBs than among those randomized to alternative drugs (odds ratio 0.90, 95% CI 0.84–0.97; $P = .006$), whereas the effect of non-dihydropyridine CCBs did not achieve significance (odds ratio 0.92, 95% CI 0.81–1.04). In a meta-regression analysis of these trials, the protection from stroke conferred by CCBs appeared unrelated to the degree of systolic blood pressure reduction.

Conclusions: These findings suggest that CCBs decrease the risk of stroke more effectively than other treatments in patients with essential hypertension and that such an effect might not be completely explained by a better antihypertensive response. Calcium channel blockers should be considered in hypertensive subjects at increased risk of stroke. Am J Hypertens 2004;17:817–822 © 2004 American Journal of Hypertension, Ltd.

Key Words: Stroke, hypertension, calcium channel blockers, therapy, prevention.

Hypertension is a potent risk factor for fatal and nonfatal strokes.[1–4] In a pooled analysis of 61 prospective studies including about one million of individuals, the risk of stroke increased progressively with blood pressure (BP) from values as low as 115/75 mm Hg without any evidence of a threshold.[5] Such relation was consistent at all ages.[5] Blood pressure lowering strongly reduces the risk of stroke,[6–8] but the possibility that specific drugs may prevail over others for protection from stroke remains unsettled. In a meta-analysis of nine trials, calcium channel blockers (CCBs) were associated with a nonsignificant 10% lesser risk of stroke when compared with different antihypertensive drugs.[9] In another meta-analysis, CCBs provided a 13.5% reduction in the risk of stroke when compared with diuretics and β-blockers.[7] In the second cycle of analyses issued by the Blood Pressure Lowering Treatment Trials Collaboration (BPLTTC), there was a trend toward a greater reduction in the risk of stroke with regimens based on CCBs than with regimens based on angiotensin-converting enzyme inhibitors (ACEIs) (12% reduction) or diuretics and/or β-blockers (7% reduction), but none of these differences achieved statistical significance.[8]

From a clinical standpoint, it may be useful to establish whether or not CCBs provide a greater protection from stroke when compared with alternative antihypertensive treatments, regardless of their type. The present overview addressed this research question.

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Table 1. Characteristics of trials included in the meta-analysis

	ABCD	ALLHAT	ALLHAT	CONVINCE	ELSA	FACET	INSIGHT
Year	1998	2002	2002	2002	2002	1998	2000
Age (y)	57	67	67	66	56	63	65
Treatment							
CCB	Nisoldipine	Amlodipine	Amlodipine	Verapamil	Lacidipine	Amlodipine	Nifedipine
Reference drugs	ACE-I	Diuretics	ACE-I	β-Blockers Diuretics	β-Blockers	ACE-I	Diuretics
Number of patients							
CCB	235	9048	9048	8179	1177	191	3157
Others	235	15255	9054	8297	1157	189	3164
Number of strokes							
CCB	11	377	377	133	9	10	67
Others	7	675	457	118	14	4	74
ΔSBP (mm Hg)	0	−1.1	1.4	0.1	0.6	6	0
Follow-up (y)	5.0	4.9	4.9	3.0	3.8	2.5	3.5

ACE-I = angiotensin-converting enzyme inhibitor; CCB = calcium channel blockers; Δ SBP = baseline-corrected differences in systolic blood pressure between CCB and reference treatment.

Methods

We selected studies that met all of the following prespecified criteria: 1) publication in peer-reviewed journals indexed in Medline; 2) inclusion of patients with clinical diagnosis of essential hypertension; 3) occurrence of stroke, as a prespecified end point, during follow-up; 4) definition of stroke events in single studies; 5) assessment of BP at baseline and follow-up visits; 6) randomized controlled comparison of regimens based on CCBs with regimens not based on CCBs; 7) follow-up of at least 2 years; and 8) sample size of 100 subjects or more.

Studies were identified through Medline using research Methodology Filters[10] with a publication date before December 15, 2003. The final search identified 13 studies[11–23] that fulfilled inclusion criteria (see Appendix for trial names). We accepted the definition of stroke events as reported in the individual reports. All outcome results were reported on the basis of an intention-to-treat approach.

The reference group comprised patients randomly assigned to other antihypertensive drugs including diuretics, β-blockers, and ACEIs. No head-to-head comparison between CCBs and angiotensin II receptor blockers was available from the literature. The odds ratio (OR) and 95% confidence interval (CI) for stroke were calculated separately for each of the 13 trials. Pooled ORs were logarithmically transformed, weighted for the inverse of variance, and computed according to fixed-effect (FE) and random-effect (RE) models. The assumption of homogeneity between individual studies was also tested. We also used a random-effect meta-regression analysis to investigate the baseline-corrected differences in systolic BP (follow-up minus baseline) between the CCBs group and the reference group as potential effect modifier. All *P* values are for two-sided tests. Analyses were done using the Stata 7.0 package (StataCorp LP, College Station, TX).

Results

Table 1 shows the main characteristics of the clinical trials considered. The FACET[22] study enrolled patients with hypertension and type 2 diabetes and the ABCD[23] study enrolled patients with type 2 diabetes with or without hypertension. For the purpose of the present analysis, we excluded the normotensive cohort of the ABCD trial, although their BP values at entry could be compatible with antihypertensive treatment according to current guidelines.[24,25] Overall, there were 4040 incident cases of stroke, 1789 among 43,053 subjects randomized to CCBs and 2251 among the 60,740 subjects randomized to other antihypertensive drugs.

Considering the 13 trials, a pooled reduction in the risk of stroke was associated with use of CCBs (OR 0.90, 95% CI 0.84–0.96; $P = .002$ for both fixed and random effects) (Fig. 1) with no significant heterogeneity across the studies ($\chi^2 = 14.00$; df = 14; $P = .50$). Because of its large sample size, the ALLHAT study exerted a major effect on pooled estimates.

We also performed subgroup analyses of the trials with dihydropyridine CCBs (11 trials) and non-dihydropyridine CCBs (4 trials). In the first analysis, there were 3048 incident cases of stroke, 1316 among the subjects randomized to CCBs and 1732 among the subjects randomized to other antihypertensive drugs. The risk of stroke differed between subjects allocated to CCBs and subjects allocated to other drugs (FE and RE: OR 0.90, 95% CI 0.84–0.97, $P = .006$; test of heterogeneity: $\chi^2 = 9.32$, $P = .502$) (Fig. 1). In the analysis of trials with non-dihydropyridine CCBs, there were 992 incident cases of stroke, 473 among the subjects randomized to CCBs and 519 among the subjects randomized to other antihypertensive drugs. The risk of stroke did not differ between subjects allocated to CCBs and subjects allocated to different drugs (FE: OR 0.92, 95% CI 0.81–1.04, $P = .184$;

Table 1. Continued

INVEST	MIDAS	NICS	NORDIL	SHELL	STOP-2	STOP-2	VHAS
2003	1996	1999	2000	2003	1999	1999	1997
66	59	70	60	72	76	76	53
Verapamil	Isradipine	Nicardipine	Diltiazem	Lacidipine	Felodipine	Felodipine	Verapam
					Isradipine	Isardipine	
β-Blockers	Diuretics	Diuretics	β-Blockers	Diuretics	β-Blockers	ACE-I	Diuretics
			Diuretics		Diuretics		
11267	442	204	5410	942	2196	2196	707
11309	441	210	5471	940	2213	2205	707
176	6	8	159	37	207	207	5
201	3	8	196	38	237	215	4
2	−3.5	−0.7	−3.1	1.1	−0.3	−0.3	−1
5.0	3.0	4.2	4.5	3.6	5.0	5.0	2.0

RE: OR 0.93, 95% CI 0.78–1.10, $P = .39$; test of heterogeneity: $\chi^2 = 4.63$, $P = .201$) (Fig. 1).

To assess the potential association between the reduction in the risk of stroke and the degree of BP lowering, we undertook a random-effect meta-regression analysis of the log OR of stroke on the baseline-corrected differences in achieved systolic BP between the CCB group and the non-CCB group in single trials. Separate analyses assuming a linear or quadratic relationship between the differences in achieved systolic BP and the log ORs were also performed.

As shown in Fig. 2, there was no relationship between the log ORs of stroke and the changes in systolic BP. Regression models different from the linear failed to achieve significance (all $P > .05$). The estimated variation in the log OR per unit increase in the difference in

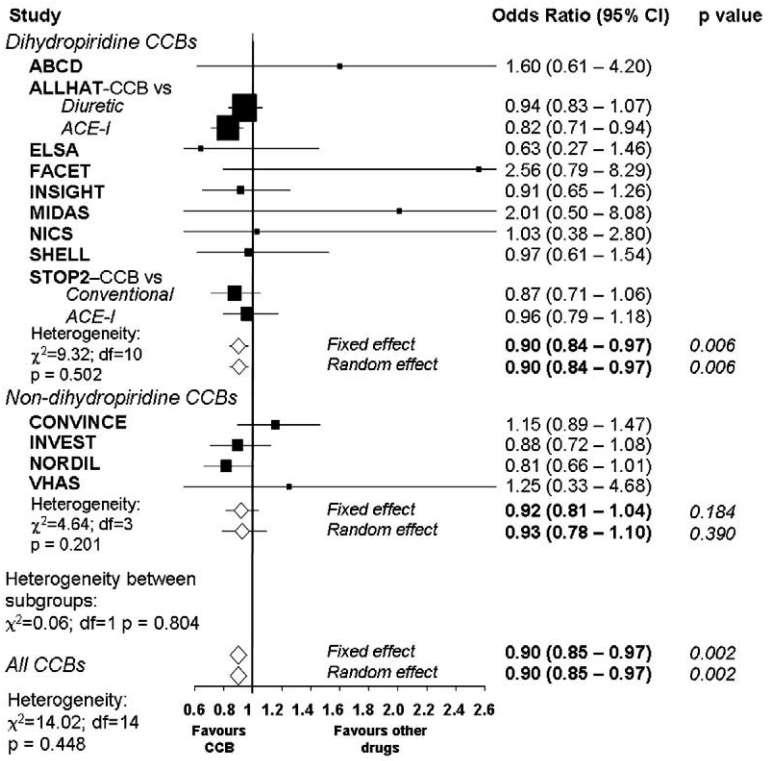

FIG. 1. Stroke events associated with calcium channel blockers (CCBs) and other drugs in patients with essential hypertension. **Black squares** represent the odds ratio in individual trials and have a size proportional to the number of events in each study. The 95% confidence intervals (CI) for individual trials are denoted by lines. **Open diamonds** represent pooled odds ratio estimates (using inverse-variance weighting). ACE-I = angiotensin-converting enzyme inhibitors; trial acronyms and references are given in the Appendix.

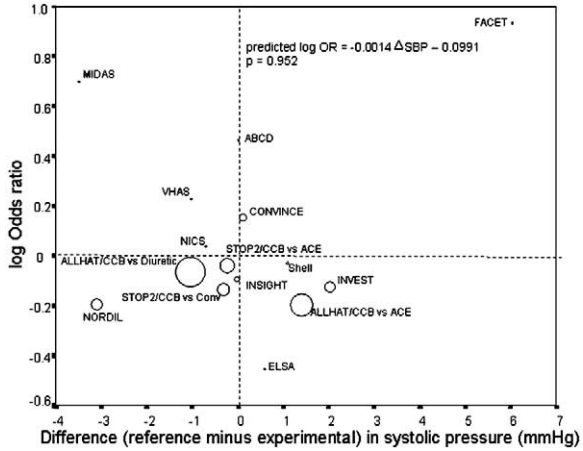

FIG. 2. Log odds ratio (OR) of stroke in 13 trials of calcium channel blockers (CCB) versus other drugs in relation to the different baseline-adjusted reduction in systolic blood pressure. The area of each circle is inversely proportional to the variance of the log odds ratio estimate. ACE = angiotensin-converting enzyme inhibitors; Conv = conventional therapy; SBP = systolic blood pressure; trial acronyms and references are given in the Appendix.

achieved systolic BP between the reference and experimental groups was only 0.014%.

Discussion

Our analysis of 13 major hypertension trials including more than 103,000 subjects and 4040 incident cases of stroke suggests that CCBs reduce the risk of stroke more effectively than other classes of antihypertensive drugs and that such an effect might be independent of the degree of BP lowering. Overall, the relative risk reduction conferred by CCBs amounted to 10% (95% CI 4–16%). Such benefit applied to the nine trials with dihydropyridine CCBs (OR 0.90, 95% CI 0.84–0.97; $P = .006$), whereas a nonsignificant 8% risk reduction was noted in the analysis of the four trials that tested non-dihydropyridine CCBs. Because the pooled effect sizes were similar, we preserve the possibility that the sample size for the latter analysis may have been too small to attain significance. Alternatively, non-dihydropyridine CCBs might be less effective than dihydropyridine CCBs in reducing the risk of stroke. Results obtained with the non-dihydropyridine CCBs were influenced by the findings of the CONVINCE study, which was stopped prematurely for nonmedical reasons and therefore was unable to satisfy the prespecified equivalence thresholds.[13] In the CONVINCE study there was a nonsignificant trend toward a higher stroke rate in the verapamil group. Of note, selectivity for vascular tissues seems to be lesser with verapamil compared with dihydropyridine and diltiazem.[26]

Comparison With Other Meta-Analyses

Our findings complete those of the second cycle of analyses by the BPLTTC group[8] with various aspects. First, our analysis did not provide separate comparisons between CCBs and either ACEIs or diuretics/β-blockers, but an overall comparison between CCBs and non-CCB agents. On the other hand, diuretics, β-blockers, and ACEIs are frequently combined and the value of these regimens for prevention of stroke as compared with regimens based on CCBs remains uncertain. Second, we added three studies (INVEST,[11] FACET,[22] and MIDAS[16]) whose designs were consistent with the hypothesis tested in our analysis and that met our inclusion criteria. Third, we excluded two studies included by the BPLTTC group because they did not meet our prespecified criteria, being carried out in purely normotensive subjects[27] or not found in the Medline database.[28] Fourth, we included separate analyses of dihydropyridine and non-dihydropyridine CCBs. Overall, the BPLTTC analysis did not preclude the possibility of a real, although moderate, effect of CCBs on the risk of stroke.[8] A recent overview[7] compared old (diuretics/β-blockers) and new (ACEIs, CCBs) antihypertensive drugs. This meta-analysis specifically compared CCBs with different drug classes on the prevention of stroke. Overall, our design resembles that of an overview by Pahor et al[9] who compared the effects of CCBs with drugs different from CCBs. In that analysis, which included 27,743 subjects, CCBs decreased the risk of stroke by 10%, as noted in our study, but the pooled estimate was not significant ($P = .10$) and the possibility of a chance effect could not be excluded. It is conceivable that our study, with its considerably larger sample size, may have had more power to detect a real difference between CCBs and non-CCBs.

Basic Mechanisms

The basic mechanisms of the protective effect of CCBs on stroke remain elusive. Experimental studies suggest a specific role of intracellular calcium in triggering ischemic cell death.[29–31] Specifically, an excessive calcium influx into depolarized neurons may contribute to the necrosis of neurons in ischemic brain area.[29–31] Novel neuronal calcium channel blockers, such as SB 201823-A, by blocking central neuronal calcium influx in vitro, reduces the ischemic injury in two rodent models of focal stroke.[32] One might speculate that CCBs currently used for antihypertensive treatment may provide some degree of neuroprotection by working through a similar mechanism. Further experimental studies are needed to evaluate whether these drugs can limit the neurologic dysfunction that follows experimental focal stroke. Moreover, randomized clinical trials should address the question of whether CCBs are able to interfere with preclinical neuronal dysfunction in patients at increased risk of stroke or Alzheimer's disease.[33] At variance with this line of thinking, administration of nimodipine, a dihydropyridine CCB, within 6 h of acute stroke was not superior to placebo on a composite outcome of death, dependency, and neurologic status.[34] The possibility that CCBs may prevent progression of carotid atherosclerosis is supported by the results of the European Lacidipine Study on Atherosclerosis, which

showed a greater efficacy of lacidipine compared to atenolol on carotid intima–media thickness progression and number of plaques per patient, despite a smaller ambulatory BP reduction.[14]

Role of BP Reduction

The reduction in BP is the main determinant in the prevention of stroke by antihypertensive drugs.[6,7] The second cycle of analyses by the BPLTTC group confirmed that the greater the difference in follow-up BP between the randomized groups, the higher the difference in the risk of stroke.[8] In the present study we investigated whether this concept applies to regimens based on CCBs compared to regimens based on drugs different from CCBs. Thus, we undertook a meta-regression analysis of trials included in the present overview to establish to what extent the BP lowering impacted on nonpooled estimates. As shown in Fig. 2, the protection from stroke conferred by CCBs appeared to be independent of the degree of systolic BP reduction. It is important to remark that all of these studies included comparisons between active drugs, in the absence of placebo treatment groups. Therefore, our meta-regression analysis was specifically designed to assess the relation between BP changes and the risk of stroke among active treatment groups, with smaller BP changes than expected if placebo-controlled studies would have been included.

Study Limitations

In most trials, a substantial proportion of patients did not continue the assigned monotherapy until the end of the study. Addition of other drugs, withdrawals of treatment, and other reasons of nonadherence to protocol may have led to an underestimation of the real differences in stroke risk between randomized groups. Furthermore, we relied on the definition and validation of stroke events reported in single studies. Although stroke was not the unique primary end point in these studies and adjudication of strokes was masked in the open trials, over- or underreporting of events cannot be ruled out. Tabular data from the examined studies did not allow differentiation between the various types of stroke, particularly between the hemorrhagic and nonhemorrhagic ones. Another limitation was that the relation between BP reduction and the risk of stroke, addressed in the meta-regression analysis, may have been affected by confounding factors.

Conclusions

The results of our overview of 13 hypertension trials, more than 103,000 subjects and 4040 incident cases of stroke, suggest that CCBs are slightly more effective than other classes of antihypertensive drugs in the prevention of stroke in patients with essential hypertension. Of particular note, such an effect seemed unrelated to the small differences in systolic BP between randomized groups. On the basis of these findings, CCBs should be considered in hypertensive subjects at increased risk for stroke on the basis of individual risk factors.[35,36]

Appendix

Trial Acronyms

ABCD = Appropriate Blood Pressure Control in Diabetes trial[23]

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[12]

CONVINCE = Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints trial[13]

ELSA = European Lacidipine Study on Atherosclerosis[14]

FACET = Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial[22]

INSIGHT = International Nifedipine GITS Study—Intervention as a Goal for Hypertension Treatment[15]

INVEST = INternational VErapamil SR/trandolapril Study[11]

MIDAS = Multicenter Isradipine Diuretic Atherosclerosis Study[16]

NICS = National Intervention Cooperative Study in Elderly Hypertensives Study Group[17]

NORDIL = NOrdic DILtiazem study[18]

SHELL = Systolic Hypertension in the Elderly Long-term Lacidipine trial[19]

STOP2 = Swedish Trial in Old Patients with hypertension-2[20]

VHAS = Verapamil in Hypertension and Atherosclerosis Study[21]

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